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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (500 characters max)

MIGFRS AS MODIFIERS OF THE IGFR PATHWAY AND METHODS OF USE

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 80
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Respectfully submitted,

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Date January 28, 2004

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Docket Number EX04-007P

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EX04-007P

MIGFRS AS MODIFIERS OF THE IGFR PATHWAY AND METHODS OF USE

BACKGROUND OF THE INVENTION

Somatic mutations in the PTEN (Phosphatase and Tensin homolog deleted on chromosome 10) gene are known to cause tumors in a variety of human tissues. In addition, germline mutations in PTEN are the cause of human diseases (Cowden disease and Bannayan-Zonana syndrome) associated with increased risk of breast and thyroid cancer (Nelen MR et al. (1997) Hum Mol Genet, 8:1383-1387; Liaw D et al. (1997) Nat Genet, 1:64-67; Marsh DJ et al. (1998) Hum Mol Genet, 3:507-515). PTEN is thought to act as a tumor suppressor by regulating several signaling pathways through the second messenger phosphatidylinositol 3,4,5 triphosphate (PIP3). PTEN dephosphorylates the D3 position of PIP3 and downregulates signaling events dependent on PIP3 levels (Maehama T and Dixon JE (1998) J Biol Chem, 22, 13375-8). In particular, pro-survival pathways downstream of the insulin-like growth factor (IGF) pathway are regulated by PTEN activity. Stimulation of the IGF pathway, or loss of PTEN function, elevates PIP3 levels and activates pro-survival pathways associated with tumorigenesis (Stambolic V et al. (1998) Cell, 95:29-39). Consistent with this model, elevated levels of insulin-like growth factors I and II correlate with increased risk of cancer (Yu H et al (1999) J Natl Cancer Inst 91:151-156) and poor prognosis (Takanami I et al, 1996, J Surg Oncol 61(3):205-8). In addition, increased levels or activity of positive effectors of the IGF pathway, such as Akt and PI(3) kinase, have been implicated in several types of human cancer (Nicholson KM and Anderson NG (2002) Cellular Signalling, 14:381-395).

In *Drosophila melanogaster*, as in vertebrates, the Insulin Growth Factor Receptor (IGFR) pathway includes the positive effectors PI(3) kinase, Akt, and PDK and the inhibitor, PTEN. These proteins have been implicated in multiple processes, including the regulation of cell growth and size as well as cell division and survival (Oldham S and Hafen E. (2003) Trends Cell Biol. 13:79-85; Garafolo RS. (2002) Trends Endocr. Metab. 13:156-162; Backman SA et al. (2002) Curr. Op. Neurobio. 12:1-7; Tapon N et al. (2001) Curr Op. Cell Biol. 13:731-737). Activation of the pathway in *Drosophila* can result in increases in cell size, cell number and organ size (Oldham S et al. (2002) Dev. 129:4103-

4109; Prober DA and Edgar BA. (2002) Genes&Dev. 16:2286-2299; Potter CJ et al. (2001) Cell 105:357-368; Verdu J et al. (1999) Cell Biol. 1:500-506).

The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as IGFR, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the IGFR pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as Modifier of IGFR (MIGFR). The invention provides methods for utilizing these IGFR modifier genes

and polypeptides to identify MIGFR-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired IGFR function and/or MIGFR function. Preferred MIGFR-modulating agents specifically bind to MIGFR polypeptides and restore IGFR function. Other preferred MIGFR-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress MIGFR gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MIGFR modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MIGFR polypeptide or nucleic acid. In one embodiment, candidate MIGFR modulating agents are tested with an assay system comprising a MIGFR polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate IGFR modulating agents. The assay system may be cell-based or cell-free. MIGFR-modulating agents include MIGFR related proteins (e.g. dominant negative mutants, and biotherapeutics); MIGFR -specific antibodies; MIGFR -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MIGFR or compete with MIGFR binding partner (e.g. by binding to an MIGFR binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate IGFR pathway modulating agents are further tested using a second assay system that detects changes in the IGFR pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the IGFR pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MIGFR function and/or the IGFR pathway in a mammalian cell by contacting the mammalian cell with

an agent that specifically binds a MIGFR polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated with the IGFR pathway.

DETAILED DESCRIPTION OF THE INVENTION

A dominant loss of function screen was carried out in *Drosophila* to identify genes that interact with or modulate the IGFR signaling pathway. Modifiers of the IGFR pathway and their orthologs were identified. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MIGFR genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective IGFR signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MIGFR function are provided herein. Modulation of the MIGFR or their respective binding partners is useful for understanding the association of the IGFR pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for IGFR related pathologies. MIGFR-modulating agents that act by inhibiting or enhancing MIGFR expression, directly or indirectly, for example, by affecting an MIGFR function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MIGFR modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

Sequences related to MIGFR nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the appended sequence listing.

The term "MIGFR polypeptide" refers to a full-length MIGFR protein or a functionally active fragment or derivative thereof. A "functionally active" MIGFR fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MIGFR protein, such as antigenic or immunogenic activity,

enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MIGFR proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MIGFR polypeptide is a MIGFR derivative capable of rescuing defective endogenous MIGFR activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an MIGFR, such as a kinase domain or a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MIGFR polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of an MIGFR. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MIGFR nucleic acid" refers to a DNA or RNA molecule that encodes a MIGFR polypeptide. Preferably, the MIGFR polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MIGFR. Methods of identifying orthlogs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res

22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and

valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in Applied Mathematics 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, Genomics 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of an MIGFR. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, Current Protocol in Molecular Biology, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of an MIGFR under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 μg/ml

herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 μg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 μg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 μg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

Isolation, Production, Expression, and Mis-expression of MIGFR Nucleic Acids and Polypeptides

MIGFR nucleic acids and polypeptides are useful for identifying and testing agents that modulate MIGFR function and for other applications related to the involvement of MIGFR in the IGFR pathway. MIGFR nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of

proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MIGFR protein for assays used to assess MIGFR function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (e.g., Higgins SJ and Hames BD (eds.) Protein Expression: A Practical Approach, Oxford University Press Inc., New York 1999; Stanbury PF et al., Principles of Fermentation Technology, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) Protein Purification Protocols, Humana Press, New Jersey, 1996; Coligan JE et al, Current Protocols in Protein Science (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MIGFR is expressed in a cell line known to have defective IGFR function. The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MIGFR polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MIGFR gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MIGFR gene product, the expression vector can comprise a promoter operably linked to an MIGFR gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MIGFR gene product based on the physical or functional properties of the MIGFR protein in *in vitro* assay systems (*e.g.* immunoassays).

The MIGFR protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (i.e. it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MIGFR gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MIGFR proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MIGFR or other genes associated with the IGFR pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

Animal models that have been genetically modified to alter MIGFR expression may be used in *in vivo* assays to test for activity of a candidate IGFR modulating agent, or to further assess the role of MIGFR in a IGFR pathway process such as apoptosis or cell proliferation. Preferably, the altered MIGFR expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MIGFR expression. The genetically modified animal may additionally have altered IGFR expression (e.g. IGFR knockout). Preferred genetically modified animals are

mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, i.e. mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (i.e., in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MIGFR gene that results in a decrease of MIGFR function, preferably such that MIGFR

expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MIGFR gene is used to construct a homologous recombination vector suitable for altering an endogenous MIGFR gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989) 244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH et al., (1994) Scan J Immunol 40:257-264; Declerck PJ et al., (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MIGFR gene, e.g., by introduction of additional copies of MIGFR, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MIGFR gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two

transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of Saccharomyces cerevisiae (O'Gorman et al. (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X et al (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the IGFR pathway, as animal models of disease and disorders implicating defective IGFR function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MIGFR function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MIGFR expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MIGFR function, animal models having defective IGFR function (and otherwise normal MIGFR function), can be used in the methods of the present invention. For example, a IGFR knockout mouse can be used to assess, *in vivo*, the activity of a candidate IGFR modulating agent identified in one of the *in vitro* assays described below. Preferably, the candidate IGFR modulating agent when administered to a model system with cells defective in IGFR function, produces a detectable phenotypic change in the model system indicating that the IGFR function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MIGFR and/or the IGFR pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the IGFR pathway, as well as in further analysis of the MIGFR protein and its contribution to the IGFR pathway. Accordingly,

the invention also provides methods for modulating the IGFR pathway comprising the step of specifically modulating MIGFR activity by administering a MIGFR-interacting or -modulating agent.

As used herein, an "MIGFR-modulating agent" is any agent that modulates MIGFR function, for example, an agent that interacts with MIGFR to inhibit or enhance MIGFR activity or otherwise affect normal MIGFR function. MIGFR function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MIGFR - modulating agent specifically modulates the function of the MIGFR. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MIGFR polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MIGFR. These phrases also encompass modulating agents that alter the interaction of the MIGFR with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MIGFR, or to a protein/binding partner complex, and altering MIGFR function). In a further preferred embodiment, the MIGFR- modulating agent is a modulator of the IGFR pathway (e.g. it restores and/or upregulates IGFR function) and thus is also a IGFR-modulating agent.

Preferred MIGFR-modulating agents include small molecule compounds; MIGFR-interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

Small molecule modulators

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight up to 10,000, preferably up to 5,000, more preferably up to

1,000, and most preferably up to 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MIGFR protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products, particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MIGFR–modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below, can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the IGFR pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MIGFR-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the IGFR pathway and related disorders, as well as in validation assays for other MIGFR-modulating agents. In a preferred embodiment, MIGFR-interacting proteins affect normal MIGFR function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MIGFR-interacting proteins are useful in detecting and providing information about the function of MIGFR proteins, as is relevant to IGFR related disorders, such as cancer (e.g., for diagnostic means).

An MIGFR-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MIGFR, such as a member of the MIGFR pathway that modulates MIGFR expression, localization, and/or activity. MIGFR-modulators include dominant negative forms of MIGFR-interacting proteins and of MIGFR proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MIGFR-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

An MIGFR-interacting protein may be an exogenous protein, such as an MIGFR-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MIGFR antibodies are further discussed below.

In preferred embodiments, an MIGFR-interacting protein specifically binds an MIGFR protein. In alternative preferred embodiments, an MIGFR-modulating agent binds an MIGFR substrate, binding partner, or cofactor.

Antibodies

In another embodiment, the protein modulator is an MIGFR specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MIGFR modulators. The antibodies can also be used in dissecting the portions of the MIGFR pathway responsible for various cellular responses and in the general processing and maturation of the MIGFR.

Antibodies that specifically bind MIGFR polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MIGFR polypeptide, and more preferably, to human MIGFR. Antibodies may be polyclonal,

monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab').sub.2 fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MIGFR which are particularly antigenic can be selected, for example, by routine screening of MIGFR polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Nati. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MIGFR. Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1}, or stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MIGFR or substantially purified fragments thereof. If MIGFR fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of an MIGFR protein. In a particular embodiment, MIGFR-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MIGFR-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MIGFR polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MIGFR polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing together genes that encode the appropriate regions from each species (Morrison et al.,

Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MIGFR-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be

produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Specific biotherapeutics

In a preferred embodiment, an MIGFR-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MIGFR is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MIGFR, as described in the previous section, may be used as biotherapeutic agents.

When the MIGFR is a receptor, its ligand(s), antibodies to the ligand(s) or the MIGFR itself may be used as biotherapeutics to modulate the activity of MIGFR in the IGFR pathway.

Nucleic Acid Modulators

Other preferred MIGFR-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MIGFR activity. Preferred nucleic acid modulators interfere with the function of the MIGFR nucleic acid such as DNA replication, transcription, translocation of the MIGFR RNA to the site of protein translation, translation of protein from the MIGFR RNA, splicing of the MIGFR RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MIGFR RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MIGFR mRNA to bind to and prevent translation, preferably by binding to the 5′ untranslated region. MIGFR-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281;

Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MIGFR nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al., Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MIGFR-specific nucleic acid modulator is used in an assay to further elucidate the role of the MIGFR in the IGFR pathway, and/or its relationship to other members of the pathway. In another aspect of the invention, an MIGFR-specific antisense oligomer is used as a therapeutic agent for treatment of IGFR-related disease states.

Assay Systems

The invention provides assay systems and screening methods for identifying specific modulators of MIGFR activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MIGFR nucleic acid or protein. In general, secondary assays further assess the activity of a MIGFR modulating agent identified by a primary assay and may confirm that the modulating agent affects MIGFR in a manner relevant to the IGFR pathway. In some cases, MIGFR modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MIGFR polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MIGFR activity, and hence the IGFR pathway. The MIGFR polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or

crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (*e.g.*, receptor-ligand binding), transcriptional activity (*e.g.*, using a reporter gene), enzymatic activity (*e.g.*, via a property of the substrate), activity of second messengers, immunogenicty and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MIGFR and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MIGFR-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MIGFR protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MIGFR-specific binding agents to function as negative effectors in MIGFR-expressing cells), binding equilibrium constants (usually at least about 10^7 M^{-1}, preferably at least about 10^8 M^{-1}, more preferably at least about 10^9 M^{-1}), and immunogenicity (e.g. ability to elicit MIGFR specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MIGFR polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MIGFR polypeptide can be full length or a fragment thereof that retains functional MIGFR activity. The MIGFR polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MIGFR polypeptide is preferably human MIGFR, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the

screening assay detects candidate agent-based modulation of MIGFR interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MIGFR –specific binding activity, and can be used to assess normal MIGFR gene function.

Suitable assay formats that may be adapted to screen for MIGFR modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (*e.g.,* Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MIGFR and IGFR pathway modulators (e.g. U.S. Pat. No. 6,165,992 (kinase assays); U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,114,132 (phosphatase and protease assays), U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein kinases, key signal transduction proteins that may be either membrane-associated or intracellular, catalyze the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein substrate. Radioassays, which monitor the transfer from [gamma-^{32}P or -^{33}P]ATP, are frequently used to assay kinase activity. For instance, a scintillation assay for p56 (lck) kinase activity monitors the transfer of the gamma phosphate from [gamma -^{33}P] ATP to a biotinylated peptide substrate. The substrate is captured on a streptavidin coated bead that transmits the signal (Beveridge M *et al.*, J Biomol Screen (2000) 5:205-212). This assay uses the scintillation proximity assay (SPA), in which only radio-ligand bound to receptors tethered to the surface of an SPA bead are detected by the scintillant immobilized within it, allowing binding to be measured without separation of bound from

free ligand. Other assays for protein kinase activity may use antibodies that specifically recognize phosphorylated substrates. For instance, the kinase receptor activation (KIRA) assay measures receptor tyrosine kinase activity by ligand stimulating the intact receptor in cultured cells, then capturing solubilized receptor with specific antibodies and quantifying phosphorylation via phosphotyrosine ELISA (Sadick MD, Dev Biol Stand (1999) 97:121-133). Another example of antibody based assays for protein kinase activity is TRF (time-resolved fluorometry). This method utilizes europium chelate-labeled anti-phosphotyrosine antibodies to detect phosphate transfer to a polymeric substrate coated onto microtiter plate wells. The amount of phosphorylation is then detected using time-resolved, dissociation-enhanced fluorescence (Braunwalder AF, et al., Anal Biochem 1996 Jul 1;238(2):159-64).

Protein phosophatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target-phosphatase increase the rate of dephosphorylation, leading to a change in polarization (Parker GJ et al., (2000) J Biomol Screen 5:77-88).

High-throughput assays, such as scintillation proximity assays, for synthase enzymes involved in fatty acid synthesis are known in the art (He X et al (2000) Anal Biochem 2000 Jun 15;282(1):107-14).

Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of

fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). Other cell-based apoptosis assays include the caspase-3/7 assay and the cell death nucleosome ELISA assay. The caspase 3/7 assay is based on the activation of the caspase cleavage activity as part of a cascade of events that occur during programmed cell death in many apoptotic pathways. In the caspase 3/7 assay (commercially available Apo-ONE™ Homogeneous Caspase-3/7 assay from Promega, cat# 67790), lysis buffer and caspase substrate are mixed and added to cells. The caspase substrate becomes fluorescent when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumalation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses an MIGFR, and that optionally has defective IGFR function (e.g. IGFR is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate IGFR modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate IGFR modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MIGFR function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MIGFR relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MIGFR plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et al.*, 1986, Int. J. Cancer 38, 369; Campana *et al.*, 1988, J. Immunol. Meth. 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specfic to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee,D.N. 1995, J. Biol. Chem 270:20098-105). Cell Proliferation may also be examined using [^{3}H]-thymidine incorporation (Chen, J., 1996, Oncogene 13:1395-403; Jeoung, J., 1995, J. Biol. Chem. 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [^{3}H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL et al., 1998, In Vitro Cell Dev Biol Anim 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook et al., Molecular Cloning, Cold Spring Harbor (1989)). For example, cells transformed with MIGFR are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Cell proliferation may also be assayed by measuring ATP levels as indicator of metabolically active cells. Such assays are commercially available, for example Cell Titer-Glo™, which is a luminescent homogeneous assay available from Promega.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW et al. (1986) Int J Radiat Biol Relat Stud Phys Chem Med 49:237-55). Cells transfected with an MIGFR may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MIGFR, and that optionally has defective IGFR function (e.g. IGFR is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate IGFR modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate IGFR modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MIGFR function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MIGFR relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MIGFR plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MIGFR, and that optionally has defective IGFR function (e.g. IGFR is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate IGFR modulating

agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate IGFR modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MIGFR function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MIGFR relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MIGFR plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glyolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MIGFR in hypoxic conditions (such as with 0.1% O2, 5% CO2, and balance N2, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses an MIGFR, and that optionally has defective IGFR function (e.g. IGFR is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate IGFR modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate IGFR modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MIGFR function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MIGFR relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MIGFR plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF , and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel™ (Becton Dickinson), an extract of basement membrane proteins

containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpa. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MIGFR's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are

fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MIGFR's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900μl of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μl of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MIGFR protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for

detecting MIGFR-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MIGFR gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MIGFR expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MIGFR) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MIGFR mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, *eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MIGFR protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MIGFR mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MIGFR-modulating agent identified by any of the above methods to confirm that the modulating agent affects MIGFR in a manner relevant to the IGFR pathway. As used herein, MIGFR-modulating agents encompass candidate clinical compounds or other agents derived from previously

identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MIGFR.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MIGFR) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MIGFR–modulating agent results in changes in the IGFR pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the IGFR or interacting pathways.

Cell-based assays

Cell based assays may detect endogenous IGFR pathway activity or may rely on recombinant expression of IGFR pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective IGFR pathway may be used to test candidate MIGFR modulators. Models for defective IGFR pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the IGFR pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, IGFR pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal IGFR are used to test the candidate modulator's affect on MIGFR in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at

4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MIGFR. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MIGFR is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, Oncogene 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MIGFR endogenously are injected in the flank, 1 x 10^5 to 1 x 10^7 cells per mouse in a volume of 100 µL using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorogenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate

modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorogenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorogenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorogenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

Diagnostic and therapeutic uses

Specific MIGFR-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the IGFR pathway, such as angiogenic, apoptotic, or cell proliferation disorders.

Accordingly, the invention also provides methods for modulating the IGFR pathway in a cell, preferably a cell pre-determined to have defective or impaired IGFR function (e.g. due to overexpression, underexpression, or misexpression of IGFR, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MIGFR activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the IGFR function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored IGFR function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired IGFR function by administering a therapeutically effective amount of an MIGFR -modulating agent that modulates the IGFR pathway. The invention further provides methods for modulating MIGFR function in a cell, preferably a cell pre-determined to have defective or impaired MIGFR function, by administering an MIGFR -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MIGFR function by administering a therapeutically effective amount of an MIGFR -modulating agent.

The discovery that MIGFR is implicated in IGFR pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the IGFR pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MIGFR expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, *eds.*, John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective IGFR signaling that express an MIGFR, are identified as amenable to treatment with an MIGFR modulating agent. In a preferred application, the IGFR defective tissue overexpresses an MIGFR

relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MIGFR cDNA sequences as probes, can determine whether particular tumors express or overexpress MIGFR. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MIGFR expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MIGFR oligonucleotides, and antibodies directed against an MIGFR, as described above for: (1) the detection of the presence of MIGFR gene mutations, or the detection of either over- or under-expression of MIGFR mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MIGFR gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MIGFR.

Kits for detecting expression of MIGFR in various samples, comprising at least one antibody specific to MIGFR, all reagents and/or devices suitable for the detection of antibodies, the immobilization of antibodies, and the like, and instructions for using such kits in diagnosis or therapy are also provided.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MIGFR expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MIGFR expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein, including an antibody.

EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. Drosophila IGFR screen

A dominant loss of function screen was carried out in *Drosophila* to identify genes that interact with or modulate the IGFR signaling pathway. Activation of the pathway by overexpression of IGFR at early stages in the developing *Drosophila* eye leads to an increase in cell number which results in a larger and rougher adult eye (Potter CJ et al. (2001) Cell 105:357-368; Huang et al., 1999. Dev. 126:5365-5372). We generated a fly stock with an enlarged eye due to overexpression of IGFR and identified modifiers of this phenotype. We then identified human orthologues of these modifiers.
The screening stock carried two transgenes. The genotype is as follows:
+; +; P{DmIGFR-pExp-UAS)} P{Gal4-pExp-1Xey}/TM6B

Screening stock females of the above genotype were crossed to males from a collection of 3 classes of piggyBac-based transposons. The resulting progeny, which contain both the transgenes and the transposon, were scored for the effect of the transposon on the eye overgrowth phenotype (either enhancement, suppression or no effect). All data was recorded and all modifiers were retested with a repeat of the original cross.

II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MIGFR symbol", and "MIGFR name aliases " provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MIGFR RefSeq_NA or GI_NA", "MIGFR GI_AA", "MIGFR NAME", and "MIGFR Description" provide the reference DNA sequences for the MIGFRs as available from National Center for Biology Information (NCBI), MIGFR protein Genbank identifier number (GI#), MIGFR name, and MIGFR description, all available from Genbank, respectively. The length of each amino acid is in the "MIGFR Protein Length" column.

Names and Protein sequences of *Drosophila* modifiers of IGFR from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by GI#, respectively.

Table 1

MIGFR symbol	MIGFR name aliases	MIGFR RefSeq_NA or GI_NA	MIGFR GI_AA	MIGFR name	MIGFR description	MIGFR protein length	Modifier name	Modifier gi_aa
NOS3	nitric oxide synthase 3 (endothelial cell)|ECNOS|eNOS|NOS3	NM_000603	40254422	nitric oxide synthase 3 (endothelial cell)	nitric oxide synthase; electron transporter; apoptosis inhibitor	1203	Nos	24583543
PRKAG1	AMPK gamma 1|PRKAG1|Protein kinase, AMP-activated, noncatalytic, gemma-1|protein kinase, AMP-activated, gamma 1 non-catalytic subunit	NM_002733	4506061	protein kinase, AMP-activated, gamma 1 non-catalytic subunit	protein kinase; protein serine/threonine kinase; protein binding	331	SNF4Agamma	24648661
PRKAG2	AAKG|AAKG2|H91620P|H91620p|H91620p protein|PRKAG2|WPWS|protein kinase, AMP-activated, gamma 2 non-catalytic subunit	NM_016203	33186925	protein kinase, AMP-activated, gamma 2 non-catalytic subunit	SNF1A/AMP-activated protein kinase; AMP binding	569	SNF4Agamma	24648661
PRKAG3	AMPK gamma 3|protein kinase, AMP-activated, gamma 3 non-catalytic subunit|PRKAG3	NM_017431	8394044	protein kinase, AMP-activated, gamma 3 non-catalytic subunit	nucleotide binding; protein binding; SNF1A/AMP-activated protein kinase	492	SNF4Agamma	24648661
NOS2A	HEP-NOS|INOS|NOS|NOS, type II|NOS2|NOS2A|nitric oxide synthase 2A (inducible, hepatocytes)|nitric oxide synthase, macrophage	NM_000625|NM_153292	24041029	nitric oxide synthase 2A (inducible, hepatocytes)	calcium channel inhibitor; nitric oxide synthase; calmodulin binding; electron transporter; antiviral response protein	1153	Nos	24583543
ITPKA	IP3K|IP3KA|IP3K-A|ITPKA|inositol 1,4,5-	NM_002220	4504789	inositol 1,4,5-trisphosphate 3-kinase A	1D-myo-inositol-trisphosphate 3-kinase	461	IP3K1	24583132

	ol 1,4,5-trisphosphate 3-kinase A			e 3-kinase A				
ITPKB	IP3 3-kinase|IP3K|IP3K B|IP3K-B|IP3KB|ITPKB|inositol 1,4,5-trisphosphate 3-kinase B	NM_002221	38569400	inositol 1,4,5-trisphosphate 3-kinase B	1D-myo-inositol-trisphosphate 3-kinase	946	IP3K1	24583132
ITPKC	IP3K C|IP3K-C|ITPKC|inositol 1,4,5-trisphosphate 3-kinase C	NM_025194	18643383	inositol 1,4,5-trisphosphate 3-kinase C	inositol/phosphatidylinositol kinase	683	IP3K1	24583132
MAN2A1	Golgi alpha-mannosidase II|mannosidase, alpha, class 2A, member 1|mannosidase, alpha type II|MANA2|MAN2A1	NM_002372	4758698	mannosidase, alpha, class 2A, member 1	mannosyl-oligosaccharide 1,3-1,6-alpha-mannosidase	1143	alpha-Man-IIb	24647249
MAN2A2	alpha-mannosidase IIX|mannosidase, alpha, class 2A, member 2|manosidase, alpha-, type II, isozyme X|mannosidase, alpha type II-X|PRO2198|MANA2X|MAN2A2	NM_006122|NM_018621	3123244	mannosidase, alpha, class 2A, member 2	alpha-mannosidase	1139	alpha-Man-IIb	24647249
NOS1	nitric oxide synthase 1 (neuronal)|NOS|NOS1	NM_000620	10835173	nitric oxide synthase 1 (neuronal)	nitric oxide synthase; electron transporter	1434	Nos	24583543
KIAA1815	FLJ23309|KIAA1815	XM_291315	37540252	KIAA1815	na	904	CG11961	24655610
POMT1	POMT1|RT|protein-O-mannosyltransferase 1	NM_007171	21361382	protein-O-mannosyltransferase 1	mannosyltransferase	747	rt	10727985

PTPRN	IA-2|IA-2/PTP|IA2|ICA 512|PTPRN|R-PTP-N|islet cell antigen 2|islet cell antigen 512|islet cell autoantigen 3|protein tyrosine phosphatase, receptor type, N|protein tyrosine phosphatase-like N precursor	NM_002846	4506321	protein tyrosine phosphatase, receptor type, N	transmembrane receptor protein tyrosine phosphatase; transmembrane receptor protein tyrosine phosphatase	979	ia2	24580758
PTPRN2	IA-2beta|IAR|IAR PTPRP|IAR/receptor-like protein-tyrosine phosphatase|ICAAR|KIAA0387|PHOGRIN|PTPRN2|PTPRP|phogrin|protein tyrosine phosphatase receptor pi|protein tyrosine phosphatase, receptor type, N polypeptide 2|tyrosine phosphatase IA-2 beta	NM_002847|NM_130842|NM_130843	11386149	protein tyrosine phosphatase, receptor type, N polypeptide 2	transmembrane receptor protein tyrosine phosphatase	1015	ia2	24580758
SYNJ1	INPP5G|SYNJ1|inositol 5'-phosphatase (synaptojanin 1)|synaptojanin 1|synaptojanin-1, polyphosphoinositide phosphatase	NM_003895	4507335	synaptojanin 1	polyphosphoinositide phosphatase; inositol-1,4,5-trisphosphate 5-phosphatase	1575	synaptojanin	18497296
SYNJ2	INPP5H|SYNJ2|inositol phosphate 5'-phosphatase 2 (synaptojanin 2)|synaptojanin 2	NM_003898	26190608	synaptojanin 2	protein binding; inositol/phosphatidylinositol phosphatase; inositol-1,4,5-trisphosphate 5-phosphatase	1496	synaptojanin	18497296

LOC284767	na|similar to dJ680N4.2 (ubiquitin-conjugating enzyme E2D 3 (homologous to yeast UBC4/5))|LOC284767	XM_209367	27485630	similar to dJ680N4.2 (ubiquitin-conjugating enzyme E2D 3 (homologous to yeast UBC4/5))	na	147	eff	24646906
LOC51619	ubiquitin-conjugating enzyme HBUCE1|LOC51619	NM_015983	8393719	ubiquitin-conjugating enzyme HBUCE1	ubiquitin conjugating enzyme; enzyme	147	eff	24646906
UBE2D2	ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast)|ubiquitin-conjugating enzyme E2-17 kDa 2|ubiquitin carrier protein|E2(17)KB2|UBCH5B|UBC4/5|PUBC1|UBC4|UBE2D2	NM_003339|NM_181838	33188456	ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast)	ubiquitin conjugating enzyme;	118	eff	24646906
UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)|ubiquitin-conjugating enzyme E2-17 kDa 3|ubiquitin carrier protein|E2(17)KB3|MGC43926|MGC5416|UBCH5C|UBC4/5|UBE2D3	NM_003340|NM_181886|NM_181887|NM_181888|NM_181889|NM_181890|NM_181891|NM_181892|NM_181893	33149322	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	ubiquitin conjugating enzyme	148	eff	24646906
LOC378372	LOC378372|na|similar to dopamine beta-hydroxylase-like	XM_353788	37539365	similar to dopamine beta-hydroxylase-like	na	451	olf413	28574720
MOXD1	DKFZP564G202|MOX|MOXD1|dJ248E1.1|monooxygenase, DBH-like 1	NM_015529	37183305	monooxygenase, DBH-like 1	dopamine-beta-monooxygenase; copper binding; monooxygenase	613	olf413	28574720

III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MIGFR peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MIGFR activity.

IV. High-Throughput In Vitro Binding Assay.

^{33}P-labeled MIGFR peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM $MgCl_2$, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate IGFR modulating agents.

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MIGFR proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at 15,000 × g for 15 min. The cell lysate is incubated with 25 μl of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel

electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Kinase assay

A purified or partially purified MIGFR is diluted in a suitable reaction buffer, e.g., 50 mM Hepes, pH 7.5, containing magnesium chloride or manganese chloride (1-20 mM) and a peptide or polypeptide substrate, such as myelin basic protein or casein (1-10 μg/ml). The final concentration of the kinase is 1-20 nM. The enzyme reaction is conducted in microtiter plates to facilitate optimization of reaction conditions by increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100 μl. The reaction is initiated by the addition of ^{33}P-gamma-ATP (0.5 μCi/ml) and incubated for 0.5 to 3 hours at room temperature. Negative controls are provided by the addition of EDTA, which chelates the divalent cation ($Mg2^{+}$ or Mn^{2+}) required for enzymatic activity. Following the incubation, the enzyme reaction is quenched using EDTA. Samples of the reaction are transferred to a 96-well glass fiber filter plate (MultiScreen, Millipore). The filters are subsequently washed with phosphate-buffered saline, dilute phosphoric acid (0.5%) or other suitable medium to remove excess radiolabeled ATP. Scintillation cocktail is added to the filter plate and the incorporated radioactivity is quantitated by scintillation counting (Wallac/Perkin Elmer). Activity is defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

VII. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardais, Genome Collaborative, and Ambion.

TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan® assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan® protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed using a 7900HT instrument.

TaqMan® reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis is prepared using a universal pool of human cDNA samples, which is a mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the standard deviation of all normal samples (i.e., Tumor – average(all normal samples) > 2 x STDEV(all normal samples)).

A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression

of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate IGFR pathway modulating agent, said method comprising the steps of:

(a) providing an assay system comprising a MIGFR polypeptide or nucleic acid;

(b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and

(c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate IGFR pathway modulating agent.

2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MIGFR polypeptide.

3. The method of Claim 2 wherein the cultured cells additionally have defective IGFR function.

4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MIGFR polypeptide, and the candidate test agent is a small molecule modulator.

5. The method of Claim 4 wherein the assay is a binding assay.

6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.

7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MIGFR polypeptide and the candidate test agent is an antibody.

8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MIGFR nucleic acid and the candidate test agent is a nucleic acid modulator.

9. The method of claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.

11. The method of Claim 1 additionally comprising:

(d) administering the candidate IGFR pathway modulating agent identified in (c) to a model system comprising cells defective in IGFR function and, detecting a phenotypic change in the model system that indicates that the IGFR function is restored.

12. The method of Claim 11 wherein the model system is a mouse model with defective IGFR function.

13. A method for modulating a IGFR pathway of a cell comprising contacting a cell defective in IGFR function with a candidate modulator that specifically binds to a MIGFR polypeptide, whereby IGFR function is restored.

14. The method of claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in IGFR function.

15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.

16. The method of Claim 1, comprising the additional steps of:

(d) providing a secondary assay system comprising cultured cells or a non-human animal expressing MIGFR ,

(e) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

(f) detecting an agent-biased activity of the second assay system,

wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate IGFR pathway modulating agent,

and wherein the second assay detects an agent-biased change in the IGFR pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.

18. The method of Claim 16 wherein the secondary assay system comprises a non-human animal.

19. The method of Claim 18 wherein the non-human animal mis-expresses a IGFR pathway gene.

20. A method of modulating IGFR pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MIGFR polypeptide or nucleic acid.

21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the IGFR pathway.

22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.

23. A method for diagnosing a disease in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with a probe for MIGFR expression;

(c) comparing results from step (b) with a control;

(d) determining whether step (c) indicates a likelihood of disease.

24. The method of claim 23 wherein said disease is cancer.

ABSTRACT OF THE DISCLOSURE

Human MIGFR genes are identified as modulators of the IGFR pathway, and thus are therapeutic targets for disorders associated with defective IGFR function. Methods for identifying modulators of IGFR, comprising screening for agents that modulate the activity of MIGFR are provided.

Nucleic Acid and Polypeptide sequences

>gi|40254421|ref|NM_000603.2| Homo sapiens nitric oxide synthase 3 (endothelial cell) (NOS3), mRNA

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>gi|5540099|ref|NM_006122.1| Homo sapiens mannosidase, alpha, class 2A, member 2 (MAN2A2), mRNA

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>gi|10835172|ref|NM_000620.1| Homo sapiens nitric oxide synthase 1 (neuronal) (NOS1), mRNA
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>gi|37540251|ref|XM_291315.2| Homo sapiens hypothetical protein
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>gi|21361381|ref|NM_007171.2| Homo sapiens protein-O-
mannosyltransferase 1 (POMT1), mRNA
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>gi|18860905|ref|NM_002846.2| Homo sapiens protein tyrosine
phosphatase, receptor type, N (PTPRN), mRNA
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>gi|19743910|ref|NM_002847.2| Homo sapiens protein tyrosine phosphatase, receptor type, N polypeptide 2 (PTPRN2), transcript variant 1, mRNA

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>gi|4507334|ref|NM_003895.1| Homo sapiens synaptojanin 1 (SYNJ1), mRNA
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>gi|26190607|ref|NM_003898.1| Homo sapiens synaptojanin 2 (SYNJ2), mRNA
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>gi|37556102|ref|XM_209367.2| Homo sapiens similar to dJ680N4.2
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(LOC284767), mRNA
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>gi|19549332|ref|NM_015983.2| Homo sapiens ubiquitin-conjugating enzyme
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>gi|33188457|ref|NM_003339.2| Homo sapiens ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast) (UBE2D2), transcript variant 1, mRNA
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>gi|33149308|ref|NM_003340.4| Homo sapiens ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast) (UBE2D3), transcript variant 1, mRNA

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TGTATATACTGTTGGGATTTGCTTCATTGTTTGACATCAAATGATGATGTAAAGTTCGAAAGAGTGAATA
TTTTGCCATGTTCAGTTAAAGTGCACAGTCTGTTACAGGTTGACACATTGCTTGACCTGATTTATGCAGA
ATTAATAAGCTATTTGGATAGTGTAGCTTTAATGTGCTGCACATGATACTGGCAGCCCTAGAGTTCATAG
ATGGACTTTTGGGACCCAGCAGTTTTGAAATGTGTTTATGGAGTTTAAGAAATTTATTTTCCAGGTGCAG
CCCCTGTCTAACTGAAATTTCTCTTCACCTTGTACACTTGACAGCTGAAAAAAAACAACATGGGAGTAAT
AATGGGTCAAAATTTGCAAAATAAAGTACTGTTTTGGTGTGGGAGTTGTCATGAGGCTGTGTTGAAGTGA
CTTATCTATGTGGGATATTGAGTATCCATTGAAATGGATTTGTTCAGCCATTTACATTAATGAGCATTTA
AATGCAACAGATATCATTTCAGGTGACTTAACATGAATGAATAAAAGTCAATGCTATTGGAAAAAAAAAA
AAAAAA

>gi|37539364|ref|XM_353788.1| Homo sapiens similar to dopamine beta-hydroxylase-like (LOC378372), mRNA
ATGGCCCATGACCTTCTCTTCAGGCTTTTTCCACTTTTGGCCCTGGGAGTCCCCTTACAAAGCAACCGCC
TTGGCCCCACATCTCGCCTGCGCTATTCCAGGTTCCTAGATCCTTCTAATGTCATTTTCCTGCGTTGGGA
CTTTGACCTTGAGGCTGAAATCATCAGTTTTGAGCTCCAGGTCCGTACAGCTGGCTGGGTGGGCTTCGGT
GTCACAAATCGCTACACCAACGTGGGAAGTGATCTGGTTGTTGGAGGAGTCTTGCCTAATGGCAATGTCT
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GGGCCTGACGGAAGATGCTGTCTACACCACCATGCACTTTTCCAGGCCCTTCCGCTCCTGCGACCCTCAT
GACCTGGATATTACGAGCAACACCGTGAGGGTGCTGGCCGCCTATGGCCTGGATGACACTCTGAAGCTGT
ATCGGGAGCGTACTTTTGTCAAGTCCATCTTTCTGCTACAAGTCGTCCACCCTGACGATCTGGATGTCCC
TGAGGACACCATCATCCATGACTTGGAGATCACTAATTTCCTCATTCCAGAGGATGACACCACGTATGCC
TGCACCTTTCTTCCTCTCCCTATTGTGAGCGAGAAGCATCACATTTACAAGTTTGAGCCTAAGTTGGTCT
ACCACAATGAGACAACGGTGCATCACATCCTGGTGTACGCCTGTGGCAATGCTAGCGTTCTCCCCACAGG
CATCAGCGACTGCTATGGGGCCGACCCTGCCTTCTCCCTTTGCTCACAGGTCATCGTGGGCTCGGCTGTC
GGGGGCACACTGTGCAAATACGACACGGATGTCCTCCAGCTGGGCTTCTTCACGTTTCCCATCCACTTCA
TCCCCCCGGGCGCTGAGTCCTTCATGTCCTATGGGCTGTGTAGGACGGAGAAGTTTGAGGAGATGAATGG
AGCTCCTATGCCTGACATACAGGTGTATGGCTACCTGCTGCACACCCACTTGGCTGGACGGGCTCTGCAA
GCAGTGCAATACAGGAATGGAACACAACTTCGAAAAATCTGTAAAGACGATTCCTATGACTTCAACCTGC
AGGAGACTCGAGATTTGCCCTCTAGAGTGGAGATCAAGCCGGGAGATGAATTGCTGGTAGAATGTCACTA
CCAGACACTGGACCGTGACTCCATGACATTTGGAGGCCCCAGCACCATTAATGAGATGTGCCTCATCTTC
CTCTTCTACTATCCCCAAAATAACATCTCCAGCTGCATGGGGTACCCTGACATTATCTACGTGGCCCACG

AGCTAGGGGAGGAGGCATCAGAGTGA

>gi|24308084|ref|NM_015529.1| Homo sapiens monooxygenase, DBH-like 1 (MOXD1), mRNA

TTTCCAAGGAAGGAAAGGCACACAATGGTATCAAATGTTCATTCATTCCATCTCTTGATGCTCTACGATA
TTATCAGTCTACACTATGCTTTCCTGAAAGGCCAGAAGTTCAAAGATGGACTAGTTTCCCAGGGACCTGA
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TTTGTCTTTAAAGGTCCTATGAATTCTTTTCTCTCTGTATTTAGGTATCCTGATTTTTCTTTTCCATATT
TTCCACAGGATTATTTTACAAATGCAAATAGAGAGTTGAAAAAAGATGCTCAGCAAGATTACCATCTAGA
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GACAAGAGTATAACGGATAGCACTGTGAGAGTGATCTGGGCCTACCACCATGAAGATGCAGGAGAAGCTG
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TATTGGTGCCAAATGTTTAAGATTCCTGTGTTCCAAGAAAAGCATCATGTAATAAAGGTTGAGCCAGTGA
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CGTTCTGGAGTCCGGCCACGAGTGCTATCACCCCAACATGCCCGATGCATTCCTCACCTGTGAAACTGTG
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GAGATAACCTAATTACTGAGTGTCGCTACAACACGAAAGATAGAGCTGAGATGACTTGGGGAGGACTAAG
CACCAGGAGTGAAATGTGTCTCTCATACCTTCTTTATTACCCAAGAATTAATCTTACTCGATGTGCAAGT
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ACAGACAATGCTGAGTGGTCGATTCAAGGAATGACAGCATTACCTCCAGATATAGAAAGACCCTATAAAG
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TTGCCTTCTGCTACTCAGCTGCACGCTGAGCACCAAGAGCTTGTGATCAAAATTCTGTTGGACTTGACAA
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TGTGGAGACTTTTCTTCCCCATTTTCCCTCCCTCCTTTTTCCTTTCCATGTTACATGAGAGACATCAATC
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TGTTGGTACCCCAAATGACCCCACACCCATYTTAAAGTACTTTTTTTCACCTTCCCTGTTTAGTACTGGC
CAGATGAGTTTTTTCTAGAGCTCTGTCACTATCTGAAAAGAAAGAGGCTATGGGAAACATAGAAATGGTA
TGTATTAATAACTGATCATAGGCTGAGGAGAAAAAATGTAGCTGGCTGCAAACCCAGTGCTGTGAGGTGA
CTTATATGAGGTTCCAGATCAAAGACAGGCCGTGTGAGCCAGTCCAGGAGGGTGTAAGTTCTGAATGGTT
CCTTGCTGACTTTGGGTGACACATGTACCACATACTGGCTCAGTTTAAGTCATGGTTCTATTGTAGATTT
ATTTTTATATTAGTTAATAAATGACTTTAAATTGTCACCAATTGAAAATCTTGTCACTCTTTTGGTTTTC
TTTATATAGCTCAGCCAAATCTCTGTTTTATGTCCTGTCCTCATCTCTTAAGCTAAATCTGTTTGGATCA
TATTAATAAACCTCGTGCCG

>gi|40254422|ref|NP_000594.2| nitric oxide synthase 3 (endothelial cell) [Homo sapiens]

MGNLKSVAQEPGPPCGLGLGLGLGLCGKQGPATPAPEPSRAPASLLPPAPEHSPPSSPLTQPPEGPKFPR
VKNWEVGSITYDTLSAQAQQDGPCTPRRCLGSLVFPRKLQGRPSPGPPAPEQLLSQARDFINQYYSSIKR
SGSQAHEQRLQEVEAEVAATGTYQLRESELVFGAKQAWRNAPRCVGRIQWGKLQVFDARDCRSAQEMFTY
ICNHIKYATNRGNLRSAITVFPQRCPGRGDFRIWNSQLVRYAGYRQQDGSVRGDPANVEITELCIQHGWT
PGNGRFDVLPLLLQAPDDPPELFLLPPELVLEVPLEHPTLEWFAALGLRWYALPAVSNMLLEIGGLEFPA

APFSGWYMSTEIGTRNLCDPHRYNILEDVAVCMDLDTRTTSSLWKDKAAVEINVAVLHSYQLAKVTIVDH
HAATASFMKHLENEQKARGGCPADWAWIVPPISGSLTPVFHQEMVNYFLSPAFRYQPDPWKGSAAKGTGI
TRKKTFKEVANAVKISASLMGTVMAKRVKATILYGSETGRAQSYAQQLGRLFRKAFDPRVLCMDEYDVVS
LEHETLVLVVTSTFGNGDPPENGESFAAALMEMSGPYNSSPRPEQHKSYKIRFNSISCSDPLVSSWRRKR
KESSNTDSAGALGTLRFCVFGLGSRAYPHFCAFARAVDTRLEELGGERLLQLGQGDELCGQEEAFRGWAQ
AAFQAACETFCVGEDAKAAARDIFSPKRSWKRQRYRLSAQAEGLQLLPGLIHVHRRKMFQATIRSVENLQ
SSKSTRATILVRLDTGGQEGLQYQPGDHIGVCPPNRPGLVEALLSRVEDPPAPTEPVAVEQLEKGSPGGP
PPGWVRDPRLPPCTLRQALTFFLDITSPPSPQLLRLLSTLAEEPREQQELEALSQDPRRYEEWKWFRCPT
LLEVLEQFPSVALPAPLLLTQLPLLQPRYYSVSSAPSTHPGEIHLTVAVLAYRTQDGLGPLHYGVCSTWL
SQLKPGDPVPCFIRGAPSFRLPPDPSLPCILVGPGTGIAPFRGFWQERLHDIESKGLQPTPMTLVFGCRC
SQLDHLYRDEVQNAQQRGVFGRVLTAFSREPDNPKTYVQDILRTELAAEVHRVLCLERGHMFVCGDVTMA
TNVLQTVQRILATEGDMELDEAGDVIGVLRDQQRYHEDIFGLTLRTQEVTSRIRTQSFSLQERQLRGAVP
WAFDPPGSDTNSP

>gi|4506061|ref|NP_002724.1| protein kinase, AMP-activated, gamma 1
non-catalytic subunit; AMPK gamma 1; Protein kinase, AMP-activated,
noncatalytic, gemma-1 [Homo sapiens]
METVISSDSSPAVENEHPQETPESNNSVYTSFMKSHRCYDLIPTSSKLVVFDTSLQVKKAFFALVTNGVR
AAPLWDSKKQSFVGMLTITDFINILHRYYKSALVQIYELEEHKIETWREVYLQDSFKPLVCISPNASLFD
AVSSLIRNKIHRLPVIDPESGNTLYILTHKRILKFLKLFITEFPKPEFMSKSLEELQIGTYANIAMVRTT
TPVYVALGIFVQHRVSALPVVDEKGRVVDIYSKFDVINLAAEKTYNNLDVSVTKALQHRSHYFEGVLKCY
LHETLETIINRLVEAEVHRLVVVDENDVVKGIVSLSDILQALVLTGGEKKP

>gi|33186925|ref|NP_057287.2| protein kinase, AMP-activated, gamma 2
non-catalytic subunit; H91620p protein [Homo sapiens]
MGSAVMDTKKKKDVSSPGGSGGKKNASQKRRSLRVHIPDLSSFAMPLLDGDLEGSGKHSSRKVDSPFGPG
SPSKGFFSRGPQPRPSSPMSAPVRPKTSPGSPKTVFPFSYQESPPRSPRRMSFSGIFRSSSKESSPNSNP
ATSPGGIRFFSRSRKTSGLSSSPSTPTQVTKQHTFPLESYKHEPERLENRIYASSSPPDTGQRFCPSSFQ
SPTRPPLASPTHYAPSKAAALAAALGPAEAGMLEKLEFEDEAVEDSESGVYMRFMRSHKCYDIVPTSSKL
VVFDTTLQVKKAFFALVANGVRAAPLWESKKQSFVGMLTITDFINILHRYYKSPMVQIYELEEHKIETWR
ELYLQETFKPLVNISPDASLFDAVYSLIKNKIHRLPVIDPISGNALYILTHKRILKFLQLFMSDMPKPAF
MKQNLDELGIGTYHNIAFIHPDTPIIKALNIFVERRISALPVVDESGKVVDIYSKFDVINLAAEKTYNNL
DITVTQALQHRSQYFEGVVKCNKLEILETIVDRIVRAEVHRLVVVNEADSIVGIISLSDILQALILTPAG
AKQKETETE

>gi|8394044|ref|NP_059127.1| protein kinase, AMP-activated, gamma 3
non-catalytic subunit [Homo sapiens]
MEPGLEHALRRTPSWSSLGGSEHQEMSFLEQENSSSWPSPAVTSSSERIRGKRRAKALRWTRQKSVEEGE
PPGQGEGPRSRPAAESTGLEATFPKTTPLAQADPAGVGTPPTGWDCLPSDCTASAAGSSTDDVELATEFP
ATEAWECELEGLLEERPALCLSPQAPFPKLGWDDELRKPGAQIYMRFIEEHTCYDAMATSSKLVIFDTML
EIKKAFFALVANGVRAAPLWDSKKQSFVGMLTITDFILVLHRYYRSPLVQIYEIEQHKIETWREIYLQGC
FKPLVSISPNDSLFEAVYTLIKNRIHRLPVLDPVSGNVLHILTHKRLLKFLHIFGSLLPRPSFLYRTIQD
LGIGTFRDLAVVLETAPILTALDIFVDRRVSALPVVNECGQVVGLYSRFDVIHLAAQQTYNHLDMSVGEA
LRKRTLCLEGVLSCQPHESLGEVIDRIAREQVHRLVLVDETQHLLGVVSLSDILQALVLSPAGIDPSGPE
KI

>gi|24041029|ref|NP_000616.3| nitric oxide synthase 2A isoform 1; NOS,
type II; nitric oxide synthase, macrophage [Homo sapiens]
MACPWKFLFKTKFHQYAMNGEKDINNNVEKAPCATSSPVTQDDLQYHNLSKQQNESPQPLVETGKKSPES
LVKLDATPLSSPRHVRIKNWGSGMTFQDTLHHKAKGILTCRSKSCLGSIMTPKSLTRGPRDKPTPPDELL
PQAIEFVNQYYGSFKEAKIEEHLARVEAVTKEIETTGTYQLTGDELIFATKQAWRNAPRCIGRIQWSNLQ
VFDARSCSTAREMFEHICRHVRYSTNNGNIRSAITVFPQRSDGKHDFRVWNAQLIRYAGYQMPDGSIRGD
PANVEFTQLCIDLGWKPKYGRFDVVPLVLQANGRDPELFEIPPDLVLEVAMEHPKYEWFRELELKWYALP
AVANMLLEVGGLEFPGCPFNGWYMGTEIGVRDFCDVQRYNILEEVGRRMGLETHKLASLWKDQAVVEINI
AVLHSFQKQNVTIMDHHSAAESFMKYMQNEYRSRGGCPADWIWLVPPMSGSITPVFHQEMLNYVLSPFYY
YQVEAWKTHVWQDEKRRPKRREIPLKVLVKAVLFACMLMRKTMASRVRVTILFATETGKSEALAWDLGAL
FSCAFNPKVVCMDKYRLSCLEEERLLLVVTSTFGNGDCPGNGEKLKKSLFMLKELNNKFRYAVFGLGSSM

YPRFCAFAHDIDQKLSHLGASQLTPMGEGDELSGQEDAFRSWAVQTFKAACETFDVRGKQHIQIPKLYTS
NVTWDPHHYRLVQDSQPLDLSKALSSMHAKNVFTMRLKSRQNLQSPTSSRATILVELSCEDGQGLNYLPG
EHLGVCPGNQPALVQGILERVVDGPTPHQTVRLEALDESGSYWVSDKRLPPCSLSQALTYFLDITTPPTQ
LLLQKLAQVATEEPERQRLEALCQPSEYSKWKFTNSPTFLEVLEEFPSLRVSAGFLLSQLPILKPRFYSI
SSSRDHTPTEIHLTVAVVTYHTRDGQGPLHHGVCSTWLNSLKPQDPVPCFVRNASGFHLPEDPSHPCILI
GPGTGIAPFRSFWQQRLHDSQHKGVRGGRMTLVFGCRRPDEDHIYQEEMLEMAQKGVLHAVHTAYSRLPG
KPKVYVQDILRQQLASEVLRVLHKEPGHLYVCGDVRMARDVAHTLKQLVAAKLKLNEEQVEDYFFQLKSQ
KRYHEDIFGAVFPYEAKKDRVAVQPSSLEMSAL

>gi|4504789|ref|NP_002211.1| 1D-myo-inositol-trisphosphate 3-kinase A [Homo sapiens]
MTLPGGPTGMARPGGARPCSPGLERAPRRSVGELRLLFEARCAAVAAAAAAGEPRARGAKRRGGQVPNGL
PRAPPAPVIPQLTVTAEEPDVPPTSPGPPERERDCLPAAGSSHLQQPRRLSTSSVSSTGSSSLLEDSEDD
LLSDSESRSRGNVQLEAGEDVGQKNHWQKIRTMVNLPVISPFKKRYAWVQLAGHTGSFKAAGTSGLILKR
CSEPERYCLARLMADALRGCVPAFHGVVERDGESYLQLQDLLDGFDGPCVLDCKMGVRTYLEEELTKARE
RPKLRKDMYKKMLAVDPEAPTEEEHAQRAVTKPRYMQWREGISSSTTLGFRIEGIKKADGSCSTDFKTTR
SREQVLRVFEEFVQGDEEVLRRYLNRLQQIRDTLEVSEFFRRHEVIGSSLLFVHDHCHRAGVWLIDFGKT
TPLPDGQILDHRRPWEEGNREDGYLLGLDNLIGILASLAER

>gi|38569400|ref|NP_002212.2| 1D-myo-inositol-trisphosphate 3-kinase B; IP3 3-kinase [Homo sapiens]
MAVYCYALNSLVIMNSANEMKSGGGPGPSGSETPPPPRRAVLSPGSVFSPGRGASFLFPPAESLSPEEPR
SPGGWRSGRRRLNSSSGSGSGSSGSSVSSPSWAGRLRGDRQQVVAAGTLSPPGPEEAKRKLRILQRELQN
VQVNQKVGMFEAHIQAQSSAIQAPRSPRLGRARSPSPCPFRSSSQPPGRVLVQGARSEERRTKSWGEQCP
ETSGTDSGRKGGPSLCSSQVKKGMPPLPGRAAPTGSEAQGPSAFVRMEKGIPASPRCGSPTAMEIDKRGS
PTPGTRSCLAPSLGLFGASLTMATEVAARVTSTGPHRPQDLALTEPSGRARELEDLQPPEALVERQGQFL
GSETSPAPERGGPRDGEPPGKMGKGYLPCGMPGSGEPEVGKRPEETTVSVQSAESSDSLSWSRLPRALAS
VGPEEARSGAPVGGGRWQLSDRVEGGSPTLGLLGGSPSAQPGTGNVEAGIPSGRMLEPLPCWDAAKDLKE
PQCPPGDRVGVQPGNSRVWQGTMEKAGLAWTRGTGVQSEGTWESQRQDSDALPSPELLPQDQDKPFLRKA
CSPSNIPAVIITDMGTQEDGALEETQGSPRGNLPLRKLSSSSASSTGFSSSYEDSEEDISSDPERTLDPN
SAFLHTLDQQKPRVSKSWRKIKNMVHWSPFVMSFKKKYPWIQLAGHAGSFKAAANGRILKKHCESEQRCL
DRLMVDVLRPFVPAYHGDVVKDGERYNQMDDLLADFDSPCVMDCKMGIRTYLEEELTKARKKPSLRKDMY
QKMIEVDPEAPTEEEKAQRAVTKPRYMQWRETISSTATLGFRIEGIKKEDGTVNRDFKKTKTREQVTEAF
REFTKGNHNILIAYRDRLKAIRTTLEVSPFFKCHEVIGSSLLFIHDKKEQAKVWMIDFGKTTPLPEGQTL
QHDVPWQEGNREDGYLSGLNNLVDILTEMSQDAPLA

>gi|18643383|ref|NP_079470.1| inositol 1,4,5-trisphosphate 3-kinase C [Homo sapiens]
MRRCPCRGSLNEAEAGALPAAARMGLEAPRGGRRRQPGQQRPGPGAGAPAGRPEGGGPWARTEGSSLHSE
PERAGLGPAPGTESPQAEFWTDGQTEPAAAGLGVETERPKQKTEPDRSSLRTHLEWSWSELETTCLWTET
GTDGLWTDPHRSDLQFQPEEASPWTQPGVHGPWTELETHGSQTQPERVKSWADNLWTHQNSSSLQTHPEG
ACPSKEPSADGSWKELYTDGSRTQQDIEGPWTEPYTDGSQKKQDTEAARKQPGTGGFQIQQDTDGSWTQP
STDGSQTAPGTDCLLGEPEDGPLEEPEPGELLTHLYSHLKCSPLCPVPRLIITPETPEPEAQPVGPPSRV
EGGSGGFSSASSFDESEDDVVAGGGGASDPEDRSGSKPWKKLKTVLKYSPFVVSFRKHYPWVQLSGHAGN
FQAGEDGRILKRFCQCEQRSLEQLMKDPLRPFVPAYYGMVLQDGQTFNQMEDLLADFEGPSIMDCKMGSR
TYLEEELVKARERPRPRKDMYEKMVAVDPGAPTPEEHAQGAVTKPRYMQWRETMSSTSTLGFRIEGIKKA
DGTCNTNFKKTQALEQVTKVLEDFVDGDHVILQKYVACLEELREALEISPFFKTHEVVGSSLLFVHDHTG
LAKVWMIDFGKTVALPDHQTLSHRLPWAEGNREDGYLWGLDNMICLLQGLAQS

>gi|4758698|ref|NP_002363.1| mannosidase, alpha, class 2A, member 1; mannosidase, alpha type II [Homo sapiens]
MKLSRQFTVFGSAIFCVVIFSLYLMLDRGHLDYPRNPRREGSFPQGQLSMLQEKIDHLERLLAENNEIIS
NIRDSVINLSESVEDGPKSSQSNFSQGAGSHLLPSQLSLSVDTADCLFASQSGSHNSDVQMLDVYSLISF
DNPDGGVWKQGFDITYESNEWDTEPLQVFVVPHSHNDPGWLKTFNDYFRDKTQYIFNNMVLKLKEDSRRK
FIWSEISYLSKWWDIIDIQKKDAVKSLIENGQLEIVTGGWVMPDEATPHYFALIDQLIEGHQWLENNIGV
KPRSGWAIDPFGHSPTMAYLLNRAGLSHMLIQRVHYAVKKHFALHKTLEFFWRQNWDLGSVTDILCHMMP
FYSYDIPHTCGPDPKICCQFDFKRLPGGRFGCPWGVPPETIHPGNVQSRARMLLDQYRKKSKLFRTKVLL

APLGDDFRYCEYTEWDLQFKNYQQLFDYMNSQSKFKVKIQFGTLSDFFDALDKADETQRDKGQSMFPVLS
GDFFTYADRDDHYWSGYFTSRPFYKRMDRIMESHLRAAEILYYFALRQAHKYKINKFLSSSLYTALTEAR
RNLGLFQHHDAITGTAKDWVVVDYGTRLFHSLMVLEKIIGNSAFLLILKDKLTYDSYSPDTFLEMDLKQK
SQDSLPQKNIIRLSAEPRYLVVYNPLEQDRISLVSVYVSSPTVQVFSASGKPVEVQVSAVWDTANTISET
AYEISFRAHIPPLGLKVYKILESASSNSHLADYVLYKNKVEDSGIFTIKNMINTEEGITLENSFVLLRFD
QTGLMKQMMTKEDGKHHEVNVQFSWYGTTIKRDKSGAYLFLPDGNAKPYVYTTPPFVRVTHGRIYSEVTC
FFDHVTHRVRLYHIQGIEGQSVEVSNIVDIRKVYNREIAMKISSDIKSQNRFYTDLNGYQIQPRMTLSKL
PLQANVYPMTTMAYIQDAKHRLTLLSAQSLGVSSLNSGQIEVIMDRRLMQDDNRGLEQGIQDNKITANLF
RILLEKRSAVNTEEEKKSVSYPSLLSHITSSLMNHPVIPMANKFSPTLELQGEFSPLQSSLPCDIHLVNL
RTIQSKVGNGHSNEAALILHRKGFDCRFSSKGTGLFCSTTQGKILVQKLLNKFIVESLTPSSLSLMHSPP
GTQNISEINLSPMEISTFRIQLR

>gi|3123244|sp|P49641|M2A2_HUMAN Alpha-mannosidase IIx (Mannosyl-oligosaccharide 1,3-1,6-alpha-mannosidase) (MAN IIx) (Mannosidase alpha class 2A member 2)
MKLKKQVTVCGAAIFCVAVFSLYLMLDRVQHDPTRHQNGGNFPRSQISVLQNRIEQLEQLLEENHEIISH
IKDSVLELTANAEGPPAMLPYYTVNGSWVVPPEPRPSFFSISPQDCQFALGGRGQKPELQMLTVSEELPF
DNVDGGVWRQGFDISYDPHDWDAEDLQVFVVPHSHNDPGWIKTFDKYYTEQTQHILNSMVSKLQEDPRRR
FLWAEVSFFAKWWDNINVQKRAAVRRLVGNGQLEIATGGWVMPDEANSHYFALIDQLIEGHQWLERNLGA
TPRSGWAVDPFGYSSTMPYLLRRANLTSMLIQRVHYAIKKHFAATHSLEFMWRQTWDSDSSTDIFCHMMP
FYSYDVPHTCGPDPKICCQFDFKRLPGGRINCPWKVPPRAITEANVAERAALLLDQYRKKSQLFRSNVLL
VPLGDDFRYDKPQEWDAQFFNYQRLFDFFNSRPNLHVQAQFGTLSDYFDALYKRTGVEPGARPPGFPVLS
GDFFSYADREDHYWTGYYTSRPFYKSLDRVLEAHLRGAEVLYSLAAAHARRSGLAGRYPLSDFTLLTEAR
RTLGLFQHHDAITGTAKEAVVVDYGVRLLRSLVNLKQVIIHAAHYLVLGDKETYHFDPEAPFLQVDDTRL
SHDALPERTVIQLDSSPRFVVLFNPLEQERFSMVSLLVNSPRVRVLSEEGQPLAVQISAHWSSATEAVPD
VYQVSVPVRLPALGLGVLQLQLGLDGHRTLPSSVRIYLHGRQLSVSRHEAFPLRVIDSGTSDFALSNRYM
QVWFSGLTGLLKSIRRVDEEHEQQVDMQVLVYGTRTSKDKSGAYLFLPDGEASPTSPRSPPCCVSLKALS
SQRWLRTMSTFTRRSGFTICQGWRGCLWTYHPWWTSGTTSTRSWPCTSIQTSTARVQPRRYLKKLPLQAN
FYPMPVMAYIQDAQKRLTLHTAQALGVSSLKDGQLEVILDRRLMQDDNRGLGQGLKDNKRTCNRFRLLLE
RRTVGSEVQDSHSTSYPSLLSHLTSMYLNAPALALPVARMQLPGPGLRSFHPLASSLPCDFHLLNLRTLQ
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STDVYLEPMEIATFRLRLG

>gi|10835173|ref|NP_000611.1| nitric oxide synthase 1 (neuronal) [Homo sapiens]
MEDHMFGVQQIQPNVISVRLFKRKVGGLGFLVKERVSKPPVIISDLIRGGAAEQSGLIQAGDIILAVNGR
PLVDLSYDSALEVLRGIASETHVVLILRGPEGFTTHLETTFTGDGTPKTIRVTQPLGPPTKAVDLSHQPP
AGKEQPLAVDGASGPGNGPQHAYDDGQEAGSLPHANGLAPRPPGQDPAKKATRVSLQGRGENNELLKEIE
PVLSLLTSGSRGVKGGAPAKAEMKDMGIQVDRDLDGKSHKPLPLGVENDRVFNDLWGKGNVPVVLNNPYS
EKEQPPTSGKQSPTKNGSPSKCPRFLKVKNWETEVVLTDTLHLKSTLETGCTEYICMGSIMHPSQHARRP
EDVRTKGQLFPLAKEFIDQYYSSIKRFGSKAHMERLEEVNKEIDTTSTYQLKDTELIYGAKHAWRNASRC
VGRIQWSKLQVFDARDCTTAHGMFNYICNHVKYATNKGNLRSAITIFPQRTDGKHDFRVWNSQLIRYAGY
KQPDGSTLGDPANVQFTEICIQQGWKPPRGRFDVLPLLLQANGNDPELFQIPPELVLEVPIRHPKFEWFK
DLGLKWYGLPAVSNMLLEIGGLEFSACPFSGWYMGTEIGVRDYCDNSRYNILEEVAKKMNLDMRKTSSLW
KDQALVEINIAVLYSFQSDKVTIVDHHSATESFIKHMENEYRCRGGCPADWVWIVPPMSGSITPVFHQEM
LNYRLTPSFEYQPDPWNTHVWKGTNGTPTKRRAIGFKKLAEAVKFSAKLMGQAMAKRVKATILYATETGK
SQAYAKTLCEIFKHAFDAKVMSMEEYDIVHLEHETLVLVVTSTFGNGDPPENGEKFGCALMEMRHPNSVQ
EERKSYKVRFNSVSSYSDSQKSSGDGPDLRDNFESAGPLANVRFSVFGLGSRAYPHFCAFGHAVDTLLEE
LGGERILKMREGDELCGQEEAFRTWAKKVFKAACDVFCVGDDVNIEKANNSLISNDRSWKRNKFRLTFVA
EAPELTQGLSNVHKKRVSAARLLSRQNLQSPKSSRSTIFVRLHTNGSQELQYQPGDHLGVFPGNHEDLVN
ALIERLEDAPPVNQMVKVELLEERNTALGVISNWTDELRLPPCTIFQAFKYYLDITTPPTPLQLQQFASL
ATSEKEKQRLLVLSKGLQEYEEWKWGKNPTIVEVLEEFPSIQMPATLLLTQLSLLQPRYYSISSSPDMYP
DEVHLTVAIVSYRTRDGEGPIHHGVCSSWLNRIQADELVPCFVRGAPSFHLPRNPQVPCILVGPGTGIAP
FRSFWQQRQFDIQHKGMNPCPMVLVFGCRQSKIDHIYREETLQAKNKGVFRELYTAYSREPDKPKKYVQD
ILQEQLAESVYRALKEQGGHIYVCGDVTMAADVLKAIQRIMTQQGKLSAEDAGVFISRMRDDNRYHEDIF
GVTLRTYEVTNRLRSESIAFIEESKKDTDEVFSS

>gi|37540252|ref|XP_291315.2| similar to KIAA1815 protein [Homo sapiens]
MEWGSESAAVRRHRVGVERREGAAAAPPPEREARAQEPLVDGCSGGGRTRKRSPGGSGGASRGAGTGLSE
VRAALGLALYLIALRTLVQLSLQQLVLRGAAGHRGEFDALQARDYLEHITSIGPRTTGSPENEILTVHYL
LEQIKLIEVQSNSLHKISVDVQRPTGSFSIDFLGGFTSYYDNITNVVVKLEPRDGAQHAVLANCHFDSVA
NSPGASDDAVSCSVMLEVLRVLSTSSEALHHAVIFLFNGAEENVLQASHGFITQHPWASLIRAFINLEAA
GVGGKELVFQTGPENPWLVQAYVSAAKHPFASVVAQEVFQSGIIPSDTDFRIYRDFGNIPGIDLAFIENG
YIYHTKYDTADRILTDSIQRAGDNILAVLKHLATSDMLAAASKYRHGNMVFFDVLGLFVIAYPSRIGSII
NYMVVMGVVLYLGKKFLQPKHKTGNYKKDFLCGLGITLISWFTSLVTVLIIAVFISLIGQSLSWYNHFYV
SVCLYGTATVAKIILIHTLAKRFYYMNASAQYLGEVFFDISLFVHCCFLVTLTYQGLCSAFISAVWVAFP
LLTKLCVHKDFKQHGAQGKFIAFYLLGMFIPYLYALYLIWAVFEMFTPILGRSGSEIPPDVVLASILAGC
TMILSSYFINFIYLAKSTKKTMLTLTLVCAITFLLVCSGTFFPYSSNPANPKPKRVFLQHMTRTFHDLEG
NAVKRDSGIWINGFDYTGISHITPHIPEINDSIRAHCEENAPLCGFPWYLPVHFLIRKNWYLPAPEVSPR
NPPHFRLISKEQTPWDSIKLTFEATGPSHMSFYVRAHKGSTLSQWSLGNGTPVTSKGGDYFVFYSHGLQA
SAWQFWIEVQVSEEHPEGMVTVAIAAHYLSGEDKRSPQLDALKEKFPDWTFPSAWVCTYDLFVF

>gi|21361382|ref|NP_009102.2| protein-O-mannosyltransferase 1 [Homo sapiens]
MWGFLKRPVVVTADINLSLVALTGMGLLSRLWRLTYPRAVVFDEVYYGQYISFYMKQIFFLDDSGPPFGH
MVLALGGYLGGFDGNFLWNRIGAEYSSNVPVWSLRLLPALAGALSVPMAYQIVLELHFSHCAAMGAALLM
LIKNALITQSRLMLLESVLIFFNLLAVLSYLKFFNCQKHSPFSLSWWFWLTLTGVACSCAVGIKYMGVFT
YVLVLGVAAVHAWHLLGDQTLSNVGADVQCCMRPACMGQMRMSQGVCVFCHLLARAVALLVIPVVLYLLF
FYVHLILVFRSGPHDQIMSSAFQASLEGGLARITQGQPLEVAFGSQVTLRNVFGKPVPCWLHSHQDTYPM
IYENGRGSSHQQQVTCYPFKDVNNWWIVKDPRRHQLVVSSPPRPVRHGDMVQLVHGMTTRSLNTHDVAAP
LSPHSQEVSCYIDYNISMPAQNLWRLEIVNRGSDTDVWKTILSEVRFVHVNTSAVLKLSGAHLPDWGYRQ
LEIVGEKLSRGYHGSTVWNVEEHRYGASQEQRERERELHSPAQVDVSRNLSFMARFSELQWRMLALRSDD
SEHKYSSSPLEWVTLDTNIAYWLHPRTSAQIHLLGNIVIWVSGSLALAIYALLSLWYLLRRRRNVHDLPQ
DAWLRWVLAGALCAGGWAVNYLPFFLMEKTLFLYHYLPALTFQILLLPVVLQHISDHLCRSQLQRNSFSA
LVVAWYSSACHVSNTLRPLTYGDKSLSPHELKALRWKDSWDILIRKH

>gi|4506321|ref|NP_002837.1| protein tyrosine phosphatase, receptor type, N precursor; islet cell antigen 2; islet cell antigen 512; islet cell autoantigen 3; protein tyrosine phosphatase-like N precursor [Homo sapiens]
MRRPRRPGGLGGSGGLRLLLCLLLLSSRPGGCSAVSAHGCLFDRRLCSHLEVCIQDGLFGQCQVGVGQAR
PLLQVTSPVLQRLQGVLRQLMSQGLSWHDDLTQYVISQEMERIPRLRPPEPRPRDRSGLAPKRPGPAGEL
LLQDIPTGSAPAAQHRLPQPPVGKGGAGASSSLSPLQAELLPPLLEHLLLPPQPPHPSLSYEPALLQPYL
FHQFGSRDGSRVSEGSPGMVSVGPLPKAEAPALFSRTASKGIFGDHPGHSYGDLPGPSPAQLFQDSGLLY
LAQELPAPSRARVPRLPEQGSSSRAEDSPEGYEKEGLGDRGEKPASPAVQPDAALQRLAAVLAGYGVELR
QLTPEQLSTLLTLLQLLPKGAGRNPGGVVNVGADIKKTMEGPVEGRDTAELPARTSPMPGHPTASPTSSE
VQQVPSPVSSEPPKAARPPVTPVLLEKKSPLGQSQPTVAGQPSARPAAEEYGYIVTDQKPLSLAAGVKLL
EILAEHVHMSSGSFINISVVGPALTFRIRHNEQNLSLADVTQQAGLVKSELEAQTGLQILQTGVGQREEA
AAVLPQTAHSTSPMRSVLLTLVALAGVAGLLVALAVALCVRQHARQQDKERLAALGPEGAHGDTTFEYQD
LCRQHMATKSLFNRAEGPPEPSRVSSVSSQFSDAAQASPSSHSSTPSWCEEPAQANMDISTGHMILAYME
DHLRNRDRLAKEWQALCAYQAEPNTCATAQGEGNIKKNRHPDFLPYDHARIKLKVESSPSRSDYINASPI
IEHDPRMPAYIATQGPLSHTIADFWQMVWESGCTVIVMLTPLVEDGVKQCDRYWPDEGASLYHVYEVNLV
SEHIWCEDFLVRSFYLKNVQTQETRTLTQFHFLSWPAEGTPASTRPLLDFRRKVNKCYRGRSCPIIVHCS
DGAGRTGTYILIDMVLNRMAKGVKEIDIAATLEHVRDQRPGLVRSKDQFEFALTAVAEEVNAILKALPQ

>gi|11386149|ref|NP_002838.1| protein tyrosine phosphatase, receptor type, N polypeptide 2 isoform 1 precursor; protein tyrosine phosphatase receptor pi; phogrin; tyrosine phosphatase IA-2 beta; IAR/receptor-like protein-tyrosine phosphatase [Homo sapiens]
MGPPLPLLLLLLLLLPPRVLPAAPSSVPRGRQLPGRLGCLLEEGLCGASEACVNDGVFGRCQKVPAMDFY
RYEVSPVALQRLRVALQKLSGTGFTWQDDYTQYVMDQELADLPKTYLRRPEASSPARPSKHSVGSERRYS
REGGAALANALRRHLPFLEALSQAPASDVLARTHTAQDRPPAEGDDRFSESILTYVAHTSALTYPPGPRT
QLREDLLPRTLGQLQPDELSPKVDSGVDRHHLMAALSAYAAQRPPAPPGEGSLEPQYLLRAPSRMPRPLL

APAAPQKWPSPLGDSEDPSSTGDGARIHTLLKDLQRQPAEVRGLSGLELDGMAELMAGLMQGVDHGVARG
SPGRAALGESGEQADGPKATLRGDSFPDDGVQDDDDRLYQEVHRLSATLGGLLQDHGSRLLPGALPFARP
LDMERKKSEHPESSLSSEEETAGVENVKSQTYSKDLLGQQPHSEPGAAAFGELQNQMPGPSKEEQSLPAG
AQEALSDGLQLEVQPSEEEARGYIVTDRDPLRPEEGRRLVEDVARLLQVPSSAFADVEVLGPAVTFKVSA
NVQNVTTEDVEKATVDNKDKLEETSGLKILQTGVGSKSKLKFLPPQAEQEDSTKFIALTLVSLACILGVL
LASGLIYCLRHSSQHRLKEKLSGLGGDPGADATAAYQELCRQRMATRPPDRPEGPHTSRISSVSSQFSDG
PIPSPSARSSASSWSEEPVQSNMDISTGHMILSYMEDHLKNKNRLEKEWEALCAYQAEPNSSFVAQREEN
VPKNRSLAVLTYDHSRVLLKAENSHSHSDYINASPIMDHDPRNPAYIATQGPLPATVADFWQMVWESGCV
VIVMLTPLAENGVRQCYHYWPDEGSNLYHIYEVNLVSEHIWCEDFLVRSFYLKNLQTNETRTVTQFHFLS
WYDRGVPSSSRSLLDFRRKVNKCYRGRSCPIIVHCSDGAGRSGTYVLIDMVLNKMAKGAKEIDIAATLEH
LRDQRPGMVQTKEQFEFALTAVAEEVNAILKALPQ

>gi|4507335|ref|NP_003886.1| synaptojanin 1; inositol 5'-phosphatase (synaptojanin 1); synaptojanin-1, polyphosphoinositide phosphatase [Homo sapiens]
MAFSKGFRIYHKLDPPPFSLIVETRHKEECLMFESGAVAVLSSAEKEAIKGTYSKVLDAYGLLGVLRLNL
GDTMLHYLVLVTGCMSVGKIQESEVFRVTSTEFISLRIDSSDEDRISEVRKVLNSGNFYFAWSASGISLD
LSLNAHRSMQEQTTDNRFFWNQSLHLHLKHYGVNCDDWLLRLMCGGVEIRTIYAAHKQAKACLISRLSCE
RAGTRFNVRGTNDDGHVANFVETEQVVYLDDSVSSFIQIRGSVPLFWEQPGLQVGSHRVRMSRGFEANAP
AFDRHFRTLKNLYGRQIIVNLLGSKEGEHMLSKAFQSHLKASEHAADIQMVNFDYHQMVKGGKAEKLHSV
LKPQVQKFLDYGFFYFNGSEVQRCQSGTVRTNCLDCLDRTNSVQAFLGLEMLAKQLEALGLAEKPQLVTR
FQEVFRSMWSVNGDSISKIYAGTGALEGKAKLKDGARSVTRTIQNNFFDSSKQEAIDVLLLGNTLNSDLA
DKARALLTTGSLRVSEQTLQSASSKVLKSMCENFYKYSKPKKIRVCVGTWNVNGGKQFRSIAFKNQTLTD
WLLDAPKLAGIQEFQDKRSKPTDIFAIGFEEMVELNAGNIVSASTTNQKLWAVELQKTISRDNKYVLLAS
EQLVGVCLFVFIRPQHAPFIRDVAVDTVKTGMGGATGNKGAVAIRMLFHTTSLCFVCSHFAAGQSQVKER
NEDFIEIARKLSFPMGRMLFSHDYVFWCGDFNYRIDLPNEEVKELIRQQNWDSLIAGDQLINQKNAGQVF
RGFLEGKVTFAPTYKYDLFSDDYDTSEKCRTPAWTDRVLWRRRKWPFDRSAEDLDLLNASFQDESKILYT
WTPGTLLHYGRAELKTSDHRPVVALIDIDIFEVEAEERQNIYKEVIAVQGPPDGTVLVSIKSSLPENNFF
DDALIDELLQQFASFGEVILIRFVEDKMWVTFLEGSSALNVLSLNGKELLNRTITIALKSPDWIKNLEEE
MSLEKISIALPSSTSSTLLGEDAEVAADFDMEGDVDDYSAEVEELLPQHLQPSSSSGLGTSPSSSPRTSP
CQSPTISEGPVPSLPIRPSRAPSRTPGPPSAQSSPIDAQPATPLPQKDPAQPLEPKRPPPPRPVAPPTRP
APPQRPPPPSGARSPAPTRKEFGGIGAPPSPGVARREMEAPKSPGTTRKDNIGRSQPSPQAGLAGPGPAG
YSTARPTIPPRAGVISAPQSHARASAGRLTPESQSKTSETSKGSTFLPEPLKPQAAFPPQSSLPPPAQRL
QEPLVPVAAPMPQSGPQPNLETPPQPPPRSRSSHSLPSEASSQPQVKTNGISDGKRESPLKIDPFEDLSF
NLLAVSKAQLSVQTSPVPTPDPKRLIQLPSATQSNVNTLSSVSCMPTMPPIPARSQSQENMRSSPNPFIT
GLTRTNPFSDRTAAPGNPFRAKSEESEATSWFSKEEPVTISPFPSLQPLGHNKSRASSSLDGFKDSFDLQ
GQSTLKISNPKGWVTFEEEEDFGVKGKSKSACSDLLGNQPSSFSGSNLTLNDDWNKGTNVSFCVLPSRRP
PPPPVPLLPPGTSPPVDPFTTLASKASPTLDFTER

>gi|26190608|ref|NP_003889.1| synaptojanin 2; inositol phosphate 5'-phosphatase 2 (synaptojanin 2) [Homo sapiens]
MALSKGLRLLGRLGAEGDCSVLLEARGRDDCLLFEAGTVATLAPEEKEVIKGQYGKLTDAYGCLGELRLK
SGGTSLSFLVLVTGCTSVGRIPDAEIYKITATDFYPLQEEAKEEERLIALKKILSSGVFYFSWPNDGSRF
DLTVRTQKQGDDSSEWGNSFFWNQLLHVPLRQHQVSCCDWLLKIICGVVTIRTVYASHKQAKACLVSRVS
CERTGTRFHTRGVNDDGHVSNFVETEQMIYMDDGVSSFVQIRGSVPLFWEQPGLQVGSHHLRLHRGLEAN
APAFDRHMVLLKEQYGQQVVVNLLGSRGGEEVLNRAFKKLLWASCHAGDTPMINFDFHQFAKGGKLEKLE
TLLRPQLKLHWEDFDVFTKGENVSPRFQKGTLRMNCLDCLDRTNTVQSFIALEVLHLQLKTLGLSSKPIV
DRFVESFKAMWSLNGHSLSKVFTGSRALEGKAKVGKLKDGARSMSRTIQSNFFDGVKQEAIKLLLVGDVY
GEEVADKGGMLLDSTALLVTPRILKAMTERQSEFTNFKRIRIAMGTWNVNGGKQFRSNVLRTAELTDWLL
DSPQLSGATDSQDDSSPADIFAVGFEEMVELSAGNIVNASTTNKKMWGEQLQKAISRSHRYILLTSAQLV
GVCLYIFVRPYHVPFIRDVAIDTVKTGMGGKAGNKGAVGIRFQFHSTSFCFICSHLTAGQSQVKERNEDY
KEITQKLCFPMGRNVFSHDYVFWCGDFNYRIDLTYEEVFYFVKRQDWKKLLEFDQLQLQKSSGKIFKDFH
EGAINFGPTYKYDVGSAAYDTSDKCRTPAWTDRVLWWRKKHPFDKTAGELNLLDSDLDVDTKVRHTWSPG
ALQYYGRAELQASDHRPVLAIVEVEVQEVDVGARERVFQEVSSFQGPLDATVVVNLQSPTLEEKNEFPED
LRTELMQTLGSYGTIVLVRINQGQMLVTFADSHSALSVLDVDGMKVKGRAVKIRPKTKDWLKGLREEIIR
KRDSMAPVSPTANSCLLEENFDFTSLDYESEGDILEDDEDYLVDEFNQPGVSDSELGGDDLSDVPGPTAL
APPSKSPALTKKKQHPTYKDDADLVELKRELEAVGEFRHRSPSRSLSVPNRPRPPQPPQRPPPPTGLMVK

KSASDASISSGTHGQYSILQTARLLPGAPQQPPKARTGISKPYNVKQIKTTNAQEAEAAIRCLLEARGGA
SEEALSAVAPRDLEASSEPEPTPGAAKPETPQAPPLLPRRPPPRVPAIKKPTLRRTGKPLSPEEQFEQQT
VHFTIGPPETSVEAPPVVTAPRVPPVPKPRTFQPGKAAERPSHRKPASDEAPPGAGASVPPPLEAPPLVP
KVPPRRKKSAPAAFHLQVLQSNSQLLQGLTYNSSDSPSGHPPAAGTVFPQGDFLSTSSATSPDSDGTKAM
KPEAAPLLGDYQDPFWNLLHHPKLLNNTWLSKSSDPLDSGTRSPKRDPIDPVSAGASAAKAELPPDHEHK
TLGHWVTISDQEKRTALQVFDPLAKT

>gi|27485630|ref|XP_209367.1| similar to dJ680N4.2 (ubiquitin-conjugating enzyme E2D 3 (homologous to yeast UBC4/5)) [Homo sapiens]
MALKRINKELSDLARDPPAQCSAGPVGDDMFHWQATIMGPHDRPYQGGVFFWTIRFPTDYPFKPSKVAFT
TRIYHPNINSNGSIFLDILRSQWSPALTLSKVLLSICSLLCDPNPDDPLVPEIARIYKTDRDKYNRISRE
WTQKYAM

>gi|8393719|ref|NP_057067.1| ubiquitin-conjugating enzyme HBUCE1 [Homo sapiens]
MALKRIQKELTDLQRDPPAQCSAGPVGDDLFHWQATIMGPNDSPYQGGVFFLTIHFPTDYPFKPPKVAFT
TKIYHPNINSNGSICLDILRSQWSPALTVSKVLLSICSLLCDPNPDDPLVPEIAHTYKADREKYNRLARE
WTQKYAM

>gi|33188456|ref|NP_862821.1| ubiquitin-conjugating enzyme E2D 2 isoform 2; ubiquitin carrier protein; ubiquitin-conjugating enzyme E2-17 kDa 2 [Homo sapiens]
MFHWQATIMGPNDSPYQGGVFFLTIHFPTDYPFKPPKVAFTTRIYHPNINSNGSICLDILRSQWSPALTI
SKVLLSICSLLCDPNPDDPLVPEIARIYKTDREKYNRIAREWTQKYAM

>gi|33149322|ref|NP_871621.1| ubiquitin-conjugating enzyme E2D 3 isoform 2; ubiquitin-conjugating enzyme E2-17 kDa 3; ubiquitin carrier protein [Homo sapiens]
MALKRINKELSDLARDPPAQCSAGPVGDDMFHWQATIMGPNDSPYQGGVFFLTIHFPTDYPFKPPKVAFT
TRIYHPNINSNGSICLDILRSQWSPALTISKVLLSICSLLCDPNPDDPLVPEIARIYKTDRDKYNRLARE
WTEKYAML

>gi|37539365|ref|XP_353789.1| similar to dopamine beta-hydroxylase-like [Homo sapiens]
MAHDLLFRLFPLLALGVPLQSNRLGPTSRLRYSRFLDPSNVIFLRWDFDLEAEIISFELQVRTAGWVGFG
VTNRYTNVGSDLVVGGVLPNGNVYFSDQHLVEEDTLKEDGSQDAELLGLTEDAVYTTMHFSRPFRSCDPH
DLDITSNTVRVLAAYGLDDTLKLYRERTFVKSIFLLQVVHPDDLDVPEDTIIHDLEITNFLIPEDDTTYA
CTFLPLPIVSEKHHIYKFEPKLVYHNETTVHHILVYACGNASVLPTGISDCYGADPAFSLCSQVIVGSAV
GGTLCKYDTDVLQLGFFTFPIHFIPPGAESFMSYGLCRTEKFEEMNGAPMPDIQVYGYLLHTHLAGRALQ
AVQYRNGTQLRKICKDDSYDFNLQETRDLPSRVEIKPGDELLVECHYQTLDRDSMTFGGPSTINEMCLIF
LFYYPQNNISSCMGYPDIIYVAHELGEEASE

>gi|37183305|gb|AAQ89452.1| dopamine-oxygenase [Homo sapiens]
MCCWPLLLLWGLLPGTAAGGSGRTYPHRTLLDSEGKYWLGWSQRGSQIAFRLQVRTAGYVGFGFSPTGAM
ASADIVVGGVAHGRPYLQDYFTNANRELKKDAQQDYHLEYAMENSTHTIIEFTRELHTCDINDKSITDST
VRVIWAYHHEDAGEAGPKYHDSNRGTKSLRLLNPEKTSVLSTALPYFDLVNQDVPIPNKDTTYWCQMFKI
PVFQEKHHVIKVEPVIQRGHESLVHHILLYQCSNNFNDSVLESGHECYHPNMPDAFLTCETVIFAWAIGG
EGFSYPPHVGLSLGTPLDPHYVLLEVHYDNPTYEEGLIDNSGLRLFYTMDIRKYDAGVIEAGLWVSLFHT
IPPGMPEFQSEGHCTLECLEEALEAEKPSGIHVFAVLLHAHLAGRGIRLRHFRKGKEMKLLAYDDDFDFN
FQEFQYLKEEQTILPGDNLITECRYNTKDRAEMTWGGLSTRSEMCLSYLLYYPRINLTRCASIPDIMEQL
QFIGVKEIYRPVTTWPFIIKSPKQYKNLSFMDAMNKFKWTKKEGLSFNKLVLSLPVNVRCSKTDNAEWSI
QGMTALPPDIERPYKAEPLVCGTSSSSSLHRDFSINLLVCLLLLSCTLSTKSL